

Non-specific urethritis associated with a tetracycline-resistant T-mycoplasma

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While the causes of venereally-acquired non-specific urethritis in men remain debatable, there is strong evidence that a tetracycline-sensitive infective agent is responsible for the majority of cases. Because the urethritis is abacterial, either mycoplasmas (Shepard, 1968; Ford, 1970; McCormack, Braun, Lee, Klein, and Kass, 1973) or *Chlamydia* (Dunlop, Vaughan-Jackson, Darougar, and Jones, 1972; Oriel, Reeve, Powis, Miller, and Nicol, 1972; Richmond, Hilton, and Clarke, 1972) have become the main contenders for an aetiological role and a voluminous literature supports each viewpoint. The evidence supporting T-mycoplasmas as a major cause of non-specific urethritis consists of their high isolation rate of above 60 per cent. in most studies, and their sensitivity to tetracycline and erythromycin (Shepard, Lunceford, and Baker, 1966), but resistance to lincomycin (Csonka and Spitzer, 1969) which accords with the response of the disease to these antibiotics. The present report concerns the isolation of a T-mycoplasma highly resistant to tetracycline, in a patient whose urethritis was unaffected by the antibiotic.

Case report

A 36-year-old businessman had been seen by one of us (D.K.F.) on nine occasions in the previous 15 years for non-specific urethritis. On each of these occasions there was an associated pain in the left knee and on the first five occasions the left knee was observed to be swollen and warm; on one occasion there was an associated conjunctivitis and on another the right wrist was also found to be swollen and warm. The episodes of acute arthritis, however, never lasted longer than 2 to 4 weeks. On two occasions he had minimal circinate balanitis, but at no time keratoderma blennorrhagica. Previous treatment for the urethritis had always been with tetracycline and the urethral symptoms had always cleared promptly.

In August, 1973, he complained of an urethral discharge which followed an extramarital exposure a few days previously. He had ceased to have intercourse with his wife because the marriage was breaking up. He also

complained of some pain in the left knee but this was not swollen. He was treated with tetracycline 500 mg. three times daily for 10 days and was not seen again for 2 months.

In October, 1973, he returned and stated that the discharge had never completely cleared after the previous tetracycline treatment. He denied any further exposures.

Examination

There was a moderately profuse mucopurulent discharge. Microscopical examination of the urethral smear stained by Gram's method showed many polymorphs, scattered diphtheroids, but no gonococci or yeasts. He was started on tetracycline 500 mg. three times daily.

He returned 5 days later and stated that the discharge was unaffected by the tetracycline, which he had taken as prescribed. He was found to have a moderately profuse purulent discharge. Because of the unusual circumstances, the hospital bacteriologist was called in consultation and both Gram-stained and wet preparations were examined with great care. Once again many polymorphs and a few diphtheroids were seen and both observers failed to see any trichomonads, even with phase contrast microscopy. Cultures for gonococci and other organisms using Thayer-Martin medium and blood agar were negative. Mycoplasmal cultures in broth and agar media containing 1 per cent. respectively of urea, arginine, and dextrose resulted in the isolation of a T-mycoplasma, but no other mycoplasmas. It was not possible to culture the urethral exudate for *Chlamydia*.

Progress

The patient was then treated with erythromycin 500 mg. three times daily for 10 days. When contacted by telephone 4 days after starting erythromycin he stated that the discharge was definitely improved, and 10 days later culture of urethral loop-scrappings failed to grow any T-mycoplasmas. A follow-up examination 3 weeks after starting erythromycin when the patient had held his urine for about 2 hours did not show any evidence of urethritis.

Laboratory studies

The T-mycoplasma isolate was investigated for its sensitivity to tetracycline and erythromycin *in vitro* and compared with other stock T-mycoplasmas available

TABLE Comparison of the sensitivity to tetracycline and erythromycin between the new isolate and stock *T-mycoplasmas*

Organism tested		Inhibitory concentration $\mu\text{g./ml.}$			
Original designation ^a	Serological classification of Black ^b	Tetracycline		Erythromycin in broth	
		In broth	In agar	At pH 6.6	At pH 7.0
T-23	Type II	0.25	0.75	0.5	0.5
T-27	Type III	0.25	0.75	0.5	0.5
T-Pi	Type VI	0.5	—	—	—
T-Co	Type VII	0.75	2.5	1.0	0.5
T-960	Type VIII	0.5	—	—	—
New isolate		15	80	1.0	0.5

^aStrains 23, 27, Pi, and Co isolated in author's laboratory; strain 960 isolated by Dr. Shepard^bBlack (1973)

in the laboratory. The Table shows that five representative *T-mycoplasmas* were inhibited in broth culture by tetracycline in concentrations of 0.25 to 0.75 $\mu\text{g./ml.}$, whereas the isolate under discussion was resistant to 10 $\mu\text{g./ml.}$ but sensitive to 15 $\mu\text{g./ml.}$ Under our conditions of agar culture, three stock *T-mycoplasmas* were completely inhibited by 0.75, 0.75, and 2.5 $\mu\text{g./ml.}$ of tetracycline, whereas the resistant organism was not completely inhibited by 60 $\mu\text{g./ml.}$, but was inhibited by 80 $\mu\text{g./ml.}$ The Table shows that this tetracycline-resistant isolate was not resistant to erythromycin in broth culture at starting pHs of either 6.6 or 7.0.

Discussion

T-mycoplasmas with this degree of resistance to tetracycline have not previously been reported. The presence of this tetracycline-resistant, erythromycin-sensitive organism in a patient, whose marked urethritis did not respond to tetracycline but did respond to erythromycin would strongly suggest that the organism was, in fact, the cause of the urethritis. No other cause of urethritis was found in this patient. Unfortunately, it was not possible to culture urethral material for *Chlamydia*, and, in consequence, the hypothesis that a tetracycline-resistant, erythromycin-sensitive *Chlamydia* was also present in the urethra causing urethritis, cannot be excluded.

Of the five stock organisms that were used for comparison, one (T-Co) was somewhat more resistant to tetracycline than the others but the differences were only marginal and, in contrast, the new isolate was resistant to about twenty times the concentration of tetracycline that inhibited the stock strains in either broth or agar culture. It is presumed that the organism became resistant when the patient was treated for non-specific urethritis with tetracycline in August, 1973. The mechanism whereby the organism became resistant is unknown. We have not previously observed any cases of non-specific urethritis which have been completely unaffected by 5 days of tetracycline.

Summary

A tetracycline-resistant, erythromycin-sensitive *T-mycoplasma* was isolated from a patient whose urethritis was unaffected by tetracycline 500 mg. three times daily for 5 days, but subsequently responded to erythromycin in the same daily dosage.

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Urétrite non spécifique avec présence de *T-mycoplasme* tétracyclino-résistant

SOMMAIRE

Un *T-mycoplasme* tétracyclino-résistant érythromycino-sensible fut isolé chez un malade dont l'urétrite n'avait pas été influencée par 500 mg de tétracycline donnés trois fois par jour pendant 5 jours, mais qui répondit ensuite à l'érythromycine à la même posologie journalière.